PATENT SPECIFICATION

1001822

NO DRAWINGS

1001822

Date of Application and filing Complete Specification: Aug. 16, 1961.
No. 29597/61.
Application made in Switzerland (No. 9684) on Aug. 26, 1960.
Application made in Switzerland (No. 11895) on Oct. 25, 1960.
Application made in Switzerland (No. 6432) on June 1, 1961.
Complete Specification Published: Aug. 18, 1965.

Index at acceptance:—C2 C(2A3, 2A5, 2A14, 2R17, B4A2, B4A4, B4C, B4D, B4M)
Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

Improvements in or relating to Homothiaxanthenes

SPECIFICATION NO. 1,001,822

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British Company.

D 57684/5

THE PATENT OFFICE

ERRATUM

SPECIFICATION No. 1,001,822
Amendment No. 1

Page 5, line 20, *for* "3_2" *read* "R_2"

THE PATENT OFFICE
13th September 1965

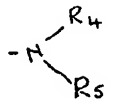
ERRATA

SPECIFICATION No. 1,001,822
Amendment No. 2

Page 4, line 59, *for* "siginfies" *read* "signifies"
Page 5, line 52, *for* "-(4')-propane" *read* "(4)-methane"

THE PATENT OFFICE
6th February 1967

each of R_4 and R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive or



R_4 together with R_5 may represents the trimethylene or tetramethylene radical, and their acid addition salts.

The invention also provides a process for the production of the compounds I above and their acid addition salts, characterised in that a 4 - hydroxy - homothiaxanthene derivative of general formula IV

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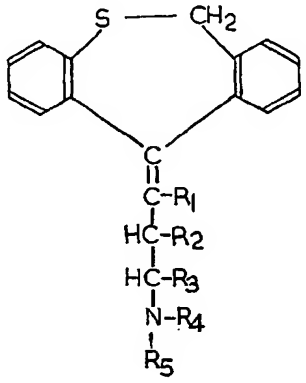
COMPLETE SPECIFICATION

Improvements in or relating to Homothiaxanthenes

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

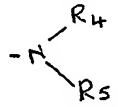
The present invention relates to novel homothiaxanthenes and processes for their production.

The present invention provides compounds of the general formula I,



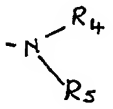
I

in which each of R_1, R_2 and R_3 signifies a hydrogen atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive and either each of R_4 and R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive or



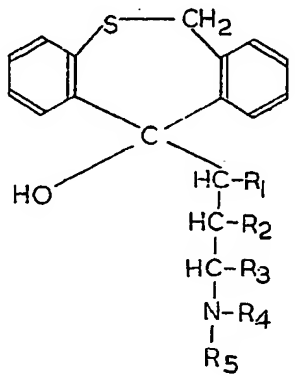
signifies the morpholino or piperidino radical, with the proviso that when two of R_1, R_2 and R_3 are hydrogen atoms, R_4 together with the remaining substituent of R_1, R_2 and R_3 may represent an alkylene radical containing from 2 to 4 carbon atoms inclusive, their acid addition salts and pharmaceutical compositions containing in addition to an inert carrier, a compound I and/or a salt thereof.

The invention further provides compounds of the general formula I in which each of R_1, R_2 and R_3 signifies a hydrogen atom or a merhyl radical, and either each of R_4 and R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or



signifies the morpholino or piperidino radical, with the proviso that when R_2 and R_3 are hydrogen atoms, R_1 together with R_4 may signify a dimethylene radical, when R_1 and R_3 are hydrogen atoms, R_2 together with R_4 may represent a dimethylene or trimethylene radical and when R_1 and R_2 signify hydrogen, R_3 together with R_4 may represents the trimethylene or tetramethylene radical, and their acid addition salts.

The invention also provides a process for the production of the compounds I above and their acid addition salts, characterised in that a 4 - hydroxy - homothiaxanthene derivative of general formula IV



IV

in which R_1 to R_5 have the above significance, is treated with a dehydrating agent so as to give said compound I and, when an acid addition salt is desired, salification is effected with an organic or inorganic acid.

Compounds IV and their production are described and claimed in the specification of our copending Application No. 1937/65 divided hereon.

The dehydration of compound IV may be effected, for example, by heating the compound IV dissolved in glacial acetic acid, with concentrated hydrochloric acid. It may, however, also be effected with phosphorus oxychloride, thionyl chloride or zinc chloride. The final product I is isolated and purified by methods known *per se*. The compounds I are oily or crystalline at room temperature. They are basic compounds and form stable salts, which are crystalline at room temperature, with inorganic or organic acids, e.g. hydrochloric, hydrobromic sulphuric, citric, oxalic, tartaric, succinic, maleic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic. The compounds I have pharmaceutical properties and are characterised by their effects on the nervous system; the exact nature of the pharmaceutical effect depends upon the nature of the basic side chain. Thus, for example, those compounds having a piperidine substituent are especially good inhibitors of histamine, serotonin and, more generally, biogenic amines, while the remaining compounds I are characterised more by their neuroplegic and anti-depressant properties.

In the following non-limitative examples all temperatures are given in degrees Centigrade, the melting and boiling points are uncorrected.

EXAMPLE 1:—

a) 4 - [1^1 - Methyl - piperidyl - (4^1)] - 4 - hydroxy - homothiaxanthene is prepared as described in Example 1 of our copending Application No. 1937/65 Serial No. 1,001,823.

b). 4 - [1^1 - Methyl - piperidylidene - (4^1)] - homothiaxanthene.

A solution of 5.0 g of 4 - [1^1 - methyl - piperidyl - (4^1)] - 4 - hydroxy - homothiaxanthene in 50 cc of glacial acetic acid is heated to the boil with 20 cc of concentrated hydrochloric acid for 1 hour. The solvent is then removed at a pressure of 15 mm of Hg, the residue made alkaline with a 20% sodium hydroxide solution and shaken three times, each time with 100 cc of ether. After washing the ether extract with water and drying over magnesium sulphate, the ether solution is concentrated to about 50 cc and saturated with hydrobromic acid gas. The ether is subsequently distilled off and the remaining oil taken up in ethanol, the 4 - [1^1 - methyl - piperidylidene - (4^1)] - homothiaxanthene - hydrobromide crystallising out in the cold. After recrystallisation from ethanol the compound melts at 265 to 270° with decomposition.

EXAMPLE 2:—

a) 4 - {β - [1^1 - Methyl - piperidyl - (2^1) - ethyl]} - 4 - hydroxy - homothiaxanthene is prepared as described in Example 2 of our copending application No. 1937/65 No. 1,001,823.

b) 1 - [1^1 - Methyl - piperidyl - (2^1)] - 2 - homothiaxanthylidene - (4^{11}) - ethane.

A solution of 10.0 g of 4 - {β - [1^1 - methyl-piperidyl - (2^1) - ethyl]} - 4 - hydroxy - homothiaxanthene in 100 cc of glacial acetic acid are heated to the boil with 40 cc of concentrated hydrochloric acid for 1 hour. The solvent is then removed at a pressure of 15 mm of Hg, the residue made alkaline with a 20% sodium hydroxide solution and shaken three times, each time with 200 cc of ether. After washing of the ether extract with water and drying over magnesium sulphate, the ether solution is concentrated to about 75 cc and saturated with hydrobromic acid gas. The ether is subsequently distilled off and the remaining oil taken up in acetone, the 1 - [1^1 - methyl - piperidyl - (2^1)] - 2 - homothiaxanthylidene - (4^{11}) - ethane crystallising in the cold. After recrystallisation from acetone the compound melts at 210 to 217° with decomposition.

EXAMPLE 3:—

a) 4 - (γ - DDiethylaminopropyl) - 4 - hydroxy - homothiaxanthene is prepared as described in Example 4 of our copending application No. 1937/65, Serial No. 1,001,823.

b) 1 - Diethylamino - 3 - homothiaxanthylidene - (4^1) - propane.

A solution of 34.0 g of 4 - (γ - diethylaminopropyl) - 4 - hydroxy - homothiaxanthene

in 150 cc of glacial acetic acid are heated to the boil with 55 cc of concentrated hydrochloric acid for 1 hour. The solvent is then removed at a pressure of 15 mm of Hg, the residue made alkaline with a 20% sodium hydroxide solution and shaken three times, each time with 200 cc of ether. After washing of the ether extract with water and drying over magnesium sulphate the ether solution is concentrated and the remaining oil distilled at 200 to 230° and 0.05 mm of Hg in an air bath. The pure 1 - diethylamino - 3 - homothiaxanthylidene - (4^1) - propane resulting as an oil is converted to the acid oxalate with oxalic acid, which after recrystallisation from ethanol melts at 174 to 176°.

EXAMPLE 4:—

a) 4 - Piperidinopropyl - 4 - hydroxy - homothiaxanthene is prepared as described in Example 5 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) 1 - Piperidino - 3 - homothiaxanthylidene-(4^1) - propane.

The dehydration is effected by heating 4 - piperidinopropyl - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid with concentrated hydrochloric acid for 1 hour in an analogous manner to Example 3. The crude 1 - piperidino - 3 - homothiaxanthylidene - (4^1) - propane obtained as an oil is converted to the hydrochloride with hydrochloric acid gas in ethanol, which melts with decomposition at 270 to 275° after recrystallisation from ethanol.

Acid fumarate, melting point 193 to 197°.

EXAMPLE 5:—

a) 4 - Morpholinopropyl - 4 - hydroxy - homothiaxanthene is prepared as described in Example 6 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) 1 - Morpholino - 3 - homothiaxanthylidene-(4^1) - propane.

The dehydration is effected by heating 4 - morpholinopropyl - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid, together with concentrated hydrochloric acid in analogous manner to that of Example 3 for one hour. The crude 1 - moropholino-3 - homothiaxanthylidene - (4^1) - propane resulting as an oil, is converted to the acid fumarate with fumaric acid which melts at 165 to 168° after recrystallisation from ethanol.

EXAMPLE 6:—

a) 4 - [(3^1 - Morpholino - 2^1 - methyl) - propyl] - 4 - hydroxy - homothiaxanthene is prepared as described in Example 7 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) 1 - Morpholino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane.

The dehydration is obtained by heating 4 - [(3^1 - morpholino - 2^1 - methyl) - propyl - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid with hydrochloric acid for one hour in an analogous manner to Example 3. The 1 - morpholino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane obtained as an oil is converted with fumaric acid to form the acid fumarate. Melting point 182 to 185° after recrystallisation from ethanol.

EXAMPLE 7:—

a) 4 - [1^1 - Methyl - piperidyl - (3^1) - methyl] - 4 - hydroxy - homothiaxanthene is prepared as described in Example 8 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) [1^1 - Methyl - piperidyl - (3^1)] - homothiaxanthylidene - (4) - methane.

The dehydration is effected by heating 4 - [1^1 - methyl - piperidyl - (3^1) - methyl] - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid with concentrated hydrochloric acid for one hour in an analogous manner to Example 3. The crude [1^1 - methyl - piperidyl-(3^1)] - homothiaxanthylidene - (4) - methane obtained as an oil is converted with fumaric acid to form the neutral fumarate. After recrystallisation from aqueous ethanol, the salt, which contains 1 mol of water of crystallisation, melts at 240 to 242°.

EXAMPLE 8:—

a) 4 - [(3^1 - Morpholino - 2^1 - methyl) - propyl] - 4 - hydroxy - homothiaxanthene is prepared as described in Example 9 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) 1 - Piperidino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane.

The dehydration is effected by heating 4 - [(3^1 - piperidino - 2^1 - methyl) - propyl] - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid with concentrated hydrochloric acid for one hour in a manner analogous to Example 3. The resulting oily residue, the crude 1 - piperidino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane, is converted with oxalic acid to the acid oxalate. After recrystallisation from ethanol the acid oxalate melts at 187 to 189°.

EXAMPLE 9:—

a) 4 - [1^1 - Methyl - pyrolidyl - (3^1) - methyl] - 4 - hydroxy - homothiaxanthene is prepared as described in Example 10 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) [1¹ - Methyl - pyrrolidyl - (3¹)] - homothiaxanthylidene - (4) - methane.

The dehydration is effected by heating 4 - [1¹ - methyl - pyrrolidyl - 3¹) - methyl] - 4 - hydroxy - homothiaxanthene dissolved in glacial acetic acid with concentrated hydrochloric acid in a manner analogous to that of Example 3. The residue obtained as an oil, the crude [1¹ - methyl - pyrrolidyl - (3¹)] - homothiaxanthylidene - (4) - methane, is converted with fumaric acid to form the neutral fumarate. After recrystallisation from ethanol/acetone the fumarate melts at 213 to 215°.

EXAMPLE 10:—

a) 4 - {β - [1¹ - Methyl - pyrrolidyl - (2¹) - ethyl]} - 4 - hydroxy - homothiaxanthene is prepared as described in Example 11 of our copending Application No. 1937/65, Serial No. 1,001,823.

b) 1 - [1¹ - Methyl - pyrrolidyl - (2¹)] - 2 - homothiaxanthylidene - (4¹¹) - ethane.

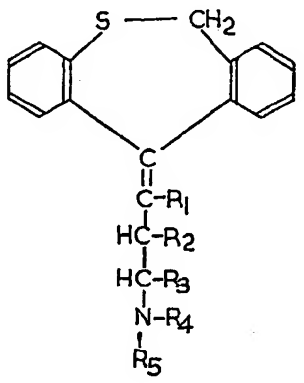
A solution of 8.0 g of 4 - {β - [1¹ - methylpyrrolidyl - (2¹) - ethyl} - 4 - hydroxy - homothiaxanthene (isomer A: melting point 192 to 200°) in 80 cc of glacial acetic acid is heated to the boil with 32 cc of concentrated hydrochloric acid for one hour. The solvent is then removed at a pressure of 15 mm of Hg, the residue made alkaline with a 2-N sodium hydroxide solution and shaken three times, each time with 200 cc of ether. After washing the ether extract with water and drying over magnesium sulphate, the solvent is removed and the oily residue, the crude 1 - [1¹ - methylpyrrolidyl - (2¹)] - 2 - homothiaxanthylidene - (4¹) - ethane, converted to the acid oxalate. After recrystallisation from ethanol/acetone the salt melts at 150 to 153°.

The dehydration from the isomer B (melting point 116 to 120°) is effected in a manner analogous to that described above. The resulting oil is treated with oxalic acid, and the resulting acid oxalate recrystallised from ethanol/acetone. The acid salt melts at 150 to 153° and is identical with the above mentioned compound.

In the Specification of our copending application No. 1939/65, Serial No. 1,001,825 there is described and claimed 1 - dimethylamino - 3 - homothiaxanthylidene - (4¹) - propane and its acid addition salts and no claim thereto is made herein.

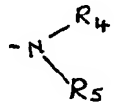
Subject to the foregoing disclaimer WHAT WE CLAIM IS:—

1. A process for the production of compounds of the general formula I,

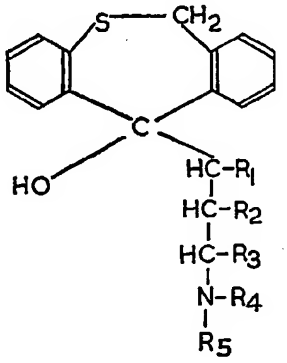


I

in which
each of R_1, R_2 and R_3 siginfies a hydrogen atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive and either each of R_1 and R_2 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or



signifies the morpholino or piperidino radical, with the proviso that when two of R_1, R_2 and R_3 are hydrogen atoms, R_4 together with the remaining substituent of R_1, R_2 and R_3 may represent an alkylene radical containing from 2 to 4 carbon atoms inclusive, and their acid addition salts, characterized in that a 4 - hydroxy - homothiaxanthene derivative of general formula IV,



IV

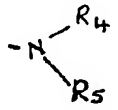
in which R_1 to R_5 have the above significance, is treated with a dehydrating agent so as to give said compound I and, when an acid addition salt is desired, salification is effected with an organic or inorganic acid.

2. A process for the production of compounds of general formula I stated in Claim 1 and their acid addition salts, substantially as herein described with reference to any one of the examples.

3. The compounds of the general formula I stated in Claim 1 and their acid addition salts, whenever produced by the process claimed in either of the preceding claims.

4. The compounds of the general formula I stated in Claim 1 and their acid addition salts.

5. Compounds of the general formula I stated in Claim 1, in which each of R_1, 3_2 and R_3 signifies a hydrogen atom or a methyl radical, and either each of R_4 and R_5 signifies an alkyl radical having from 1 to 4 carbon atoms inclusive, or



signifies the morpholino or piperidino radical, with the proviso that when R_2 and R_3 are hydrogen atoms, R_1 together with R_4 may signify a dimethylene radical, and when R_1 and R_4 are hydrogen atoms, R_2 together with R_3 may represent a dimethylene or trimethylene radical and when R_1 and R_2 signify hydrogen, R_4 together with R_5 may represent the trimethylene or tetramethylene radical, and their acid addition salts.

6. 4 - [1^1 - Methyl - piperidylidene - (4^1)] - homothiaxanthene.

7. 1 - [1^1 - Methyl - piperidyl - (2^1)] - 2 - homothiaxanthylidene - (4^{11}) - ethane.

8. 1 - Diethylamino - 3 - homothiaxanthylidene - (4^1) - propane.

9. 1 - Piperidino - 3 - homothiaxanthylidene - (4^1) - propane.

10. 1 - Morpholino - 3 - homothiaxanthylidene - (4^1) - propane.

11. 1 - Morpholino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane.

12. [1^1 - Methyl - piperidyl - (3^1)] - homothiaxanthylidene - (4) - methane.

13. 1 - Piperidino - 2 - methyl - 3 - homothiaxanthylidene - (4^1) - propane.

14. [1^1 - Methyl - pyrrolidyl - (3^1)] - homothiaxanthylidene - (4^1) - propane.

15. 1 - [1^1 - Methyl - pyrrolidyl - (2^1)] - 2 - homothiaxanthylidene - (4^{11}) - ethane.

16. The acid addition salts of the compounds claimed in claims 6 to 15.

17. Pharmaceutical compositions containing, in addition to an inert carrier, a compound claimed in any one of Claims 3 to 16.

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